Movement Disorders
CLINICAL PRACTICE
REVIEW

Epidemiology of Parkinson's Disease—East Versus West

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Abstract: **Background:** The cause of PD at present remains unknown. A number of epidemiological studies have been conducted across the globe to ascertain the disease burden and the possible risk factors. In this review, we analyze the various studies from East and West with an aim to observe the important similarities and differences in the disease occurrence and risk factor profile.
Methods: A comprehensive search of descriptive and analytical epidemiological studies was undertaken. The descriptive studies and meta-analysis providing the standardised population rates were selected. The demographics, ethnicity and geographical differences between East and West were analysed. In analytical epidemiology, more established and well-studied non-genetic risk factors for PD were reviewed utilising the prospective cohort studies, case control studies and meta-analysis where available.
Results and Conclusion: PD is more common with increasing age and shows male predominance, which is more obvious in Western studies. The PD prevalence and incidence rates are slightly lower in the East compared to the West. Incidence studies on different ethnic populations in the same country have also found a lower occurrence of PD amongst Easterners compared to Westerners. Setting methodological differences aside, studies from East and West suggest a role for both environmental and genetic risk factors in PD causation. Smoking, caffeine intake and pesticide exposure are well-established risk factors across regions. There is a robust data for dairy product consumption, urate levels and physical activity in the West while studies on certain risk factors like head injury and alcohol show conflicting and mixed results.

Parkinson's disease (PD) is the second most common neurodegenerative disorder and in the majority of cases, its cause remains unknown. Epidemiology refers to the study of distribution and determinants of health related events and their application in the control of diseases.[1]

In descriptive epidemiology, time, place, and person define the health events; while analytical epidemiology helps to identify and quantify the relationship between exposure and a particular health outcome.[1] The epidemiological studies determining race and ethnicity help us to understand the roles of, and interaction between, genetic and environmental factors in disease causation.[2]

In the present review, we analyze the epidemiological features of PD patients between Western and Eastern countries. The division of East and West is not clear, as the definition varies depending on whether historical, geographical, economic, cultural, or political factors are considered. In this review, we have adopted the cultural definition that considers Asia, and the Middle East as "Eastern" countries; Russia, Europe, the Americas, Australia, and New Zealand as "Western" countries.[3]

Descriptive Epidemiology

A Pubmed search was done for all the articles on human studies in English till May 2017 using the keywords Parkinson's disease, epidemiology, incidence, prevalence, East, West, Europe, America, and their combinations. The review articles, meta-analysis, original articles providing 2000 WHO age standardized population rates were used for comparison between East and

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Keywords: epidemiology, Parkinson's disease, risk factors.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 30 July 2017; revised 20 October 2017; accepted 2 November 2017.
Published online 22 December 2017 in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/mdc3.12568

TABLE 1 Parkinson's disease prevalence in Eastern and Western studies

Eastern studies	Crude prevalence rate (per 100,000)	Age standardized to 2000 WHO population (per 100,000)	Western studies	Crude prevalence rate (per 100,000)	Age standardized to 2000 WHO population (per 100,000)
Door-to-door surveys					
Li et al, 6 cities, China (1985)	44 (all ages) 198 (>50 years)	51.3	Tison et al, Gironde, France (1994)	1400 (>65 years)	101
Shi et al, Shanghai, China (1987)	18 (all ages)	16.8	de Rijk et al, Rotterdam, Netherlands (1995)	1400 (>55 years)	216.0
Ho et al, Hong Kong (1989)	3400 (>60 years)	440.3	de Rijk et al, (France, Italy, Netherlands, Spain) (1997)	-	135.9
Wang et al, 29 provinces, China (1991)	14.6 (all ages)	16.7	Morgante et al, Sicily, Italy (1992)	257.2 (all ages)	173.8
Zhang et al, Beijing, China (2003)	1100 (>55 years)	109.3	Benito Leon etal, Spain (2003)	1500 (>65 years)	117.6
Zhang et al, Beijing, Xian, Shanghai, China (2005)	1700 (>65 years)	176.9	Melcon et al, Argentina (1997)	656.8 (>40 years)	174.3
Chen et al, Ilan, Taiwan (2001)	367.9 (≥40 years)	113.1	Barbosa et al, Bambuí, Brazil (2006)	3,300 (>64 years)	297.7
Chen et al, Keelung, Taiwan (2009)	706 (>40 years)	193.3	Chan et al, Sydney, Australia (2005)	776 (>55 years)	439.4
Tan et al, Singapore (2004)	290 (>50 years)	61.9			
Bharucha et al, Bombay, India (1993)	328.3 (all ages)	140.6			
Das et al, Kolkata, India (2010)	40.67 (all ages)	52.85			
Anca M, Israel (2002)	240 (all ages)	113.9			
Record-based surveys					
Harada et al, Yonago, Japan (1983)	80.6 (all ages) 283 (>50 years)	68.3	Mayeux et al, New York, USA (1995)	107 (all ages)	81
Okada et al, Izumo, Japan (1990)	82 (all ages)	57.9	D'Alessandro et al, San Marino, Italy (1987)	152 (all ages)	100.4
Kusumi et al, Yonago, Japan (1996)	117.9 (all ages)	68.2	Granieri et al, Ferrara, Italy (1991)	164.75 (all ages)	95.5
Moriwaka et al, Hokkaido, Japan (1996)	94.7	61.4	Totaro et al, Central Italy (2005)	229.3 (all ages)	89.7
Kimura et al, Yamagata, Japan (2002)	118.7 (all ages)	35.8	Sutcliffe et al, Northampton, UK (1985)	108.4 (all ages)	70.9
Liu et al, Taiwan (2016)	164.1 (2002–03) 306.8 (2008–09)	159.8 (2002–03) 299.3 (2008–09)	Mutch et al, Aberdeen, Scotland, UK (1986)	164.2 (all ages)	91.4
			Shrag et al, London, UK (2000)	128 (all ages)	91.7
			Errea et al, Spain (1999)	220.6 (all ages)	93.8
			Mehta et al, Sydney, Australia (2007)	460 (>50 years)	71.3

West studies. In addition, the results of relevant meta-analysis were also discussed.

There are a number of PD descriptive epidemiology studies in the literature. The comparison of these studies remains problematic due to lack of uniformity. The PD diagnostic criteria, screening population, methods of case ascertainment varies widely leading to a large variation in prevalence and incidence rates even within the same region.[4]

The screening methods (door-to-door survey with a questionnaire, followed by examination) is ideal, but costly to perform and nonparticipation can result in sampling bias. The record-based surveys are easier to perform, but they often miss patients in early stages of disease and are dependent on health seeking behavior of the patients.[4–7] These major difficulties can be circumvented by using two-phase door-to-door surveys, identical diagnostic criteria, specialist examination, and age-

standardized rates that are calculated to a reference population.[4]

PD Prevalence

Prevalence is the number of current cases (both new and antecedent) in the population during a specified point in time (point prevalence) or over a specified period of time (period prevalence). It is influenced by the incidence and duration of illness and is a measure of disease burden in a community.[1] Table 1 summarizes the PD prevalence studies that have 2000 WHO population age standardized rates available.[4,8–10]

The overall prevalence of PD appears to be lower in the Eastern studies compared to Western ones (Fig. 1). This could be due to a combination of genetic and environmental factors, as well as methodological differences.[4–7] In a meta-analysis of 19 Asian studies from 1965 to 2008, the prevalence rate (age standardized to 2000 WHO population) was 51.3–176.9/100,000 in the door-to-door surveys, excluding an older study with a low prevalence of 16.7/10,000. The record-based studies showed a lower prevalence rate (35.8–68.3/100,000).[4] A recent meta-analysis of 15 Asian studies on Chinese (10 China, two Hong Kong, three Taiwan) showed a prevalence rate of 16–440.3/100,000 (age standardized to 2000 WHO population).[8] The older studies from China had a lower prevalence rate, however, it was higher in a study from the elderly resident homes in Hong Kong during the same period.[8] The prevalence rate increased to 79.5–193.3/1,00,000 when only studies from 1995 were considered.[8] The lower prevalence in the earlier Chinese studies could be due to the methodological differences. However, it could also be a true increase in prevalence rate, reflecting a change in environmental risk factors[11] or an ageing population. A similar increase in prevalence over time was observed in the studies from Japan[12] and Taiwan.[10,13] The prevalence rates were lower than Western populations in the studies from Japan, Singapore, and India except for a study in the Parsi community from India (Fig. 1).

In a meta-analysis of 39 European studies until 2004, the authors reported a prevalence rate of 108–257/100,000 when considering only high-quality studies that utilized a standard diagnostic criterion, inclusion of entire age group, and screening by an experienced neurologist.[7] Another meta-analysis of eight studies from England observed a prevalence of 105–178/100,000 (age standardized to 1997 England population).[14] A median prevalence of 950/100,000 was noted in people over 65 years in a review of

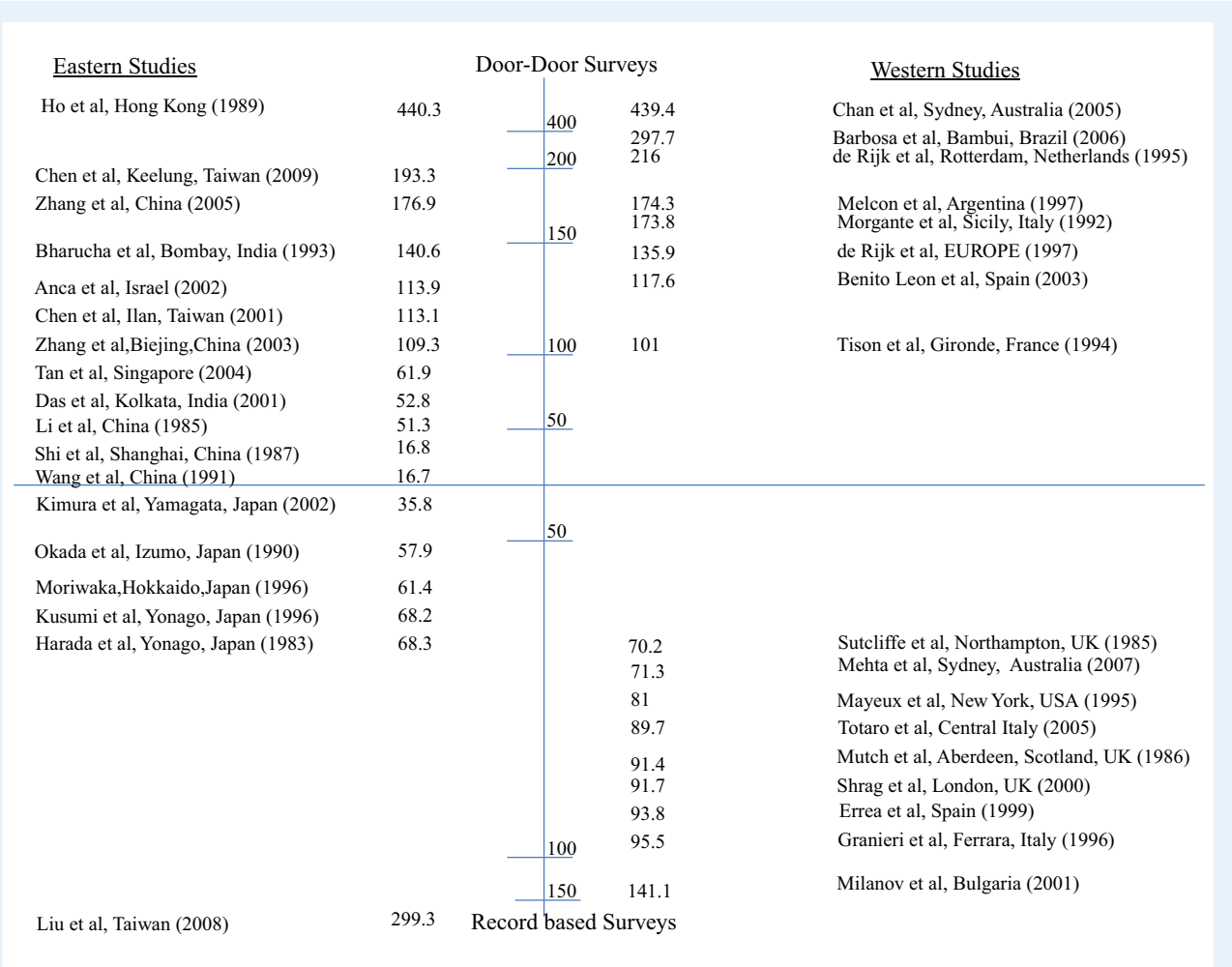

FIG. 1. Prevalence of Parkinson's disease in Eastern and Western studies age standardised to 2000 WHO population (per 1,00,000).

11 studies between 1990 to 2005 from Europe and America.[15] A prevalence of 101–439.4/100,000 and 61.4–141.1/100,000 (age standardized to 2000 WHO population) in the door-to-door and record-based surveys, respectively, were observed in the Western studies in another review.[4]

Influence of Age and Gender on PD Prevalence

Males were 1.5 to two times more affected by PD in a majority of the studies.[7] However, this was not observed in some studies[16] and others noted a female predominance.[17,18] The gender difference was less apparent in Asian studies.[4,6]

PD prevalence was high in the 7th and 8th decades across the geographical locations. In few studies, the prevalence declined in the 8th decade, following a peak in the 70–79 age groups.[17,18] In a meta-analysis, the prevalence among the age groups 70–79 years was less in Asians compared to the Western population.[6] These differences could be related to the smaller sample size, lower response rate, misdiagnosis, and different survival times.[4,8]

PD Incidence

The incidence of a disease refers to the number of new cases that develop in the population during a specific period of time. It is a measure of the probability of an event among persons at risk.[1] Table 2 summarizes the PD incidence studies that have 2000 WHO population age standardized rates available.[4,7,9,10]

The incidence of PD is lower in Asians compared to the Western population, except for a recent record-based survey from Taiwan[10] (Fig. 2). However, the number of Asian studies are limited.[4,5] In a meta-analysis of Asian studies, the incidence rate (age standardized to 2000 WHO world population) was 8.7/100,000 in the door-to-door surveys and 6.7–8.3/100,000 in the record-based studies.[4] The Western studies had a higher incidence rate of 15.4–27.6/100,000 and 6.1–17.4/100,000 in the door to door and record-based studies respectively.[4]

The incidence in Asian studies was lower at 1.5–17/100,000 compared to 9–22/100,000 and 11–13/100,000 in studies from Europe and North American studies respectively in another review.[5] A meta-analysis of 13 European studies observed a incidence of 11–19/100,000.[7] In another review of Western studies, the median incidence was 14/100,000 (range 12–15); in 65 years or older or 70 years or older population the median incidence was higher at 160/100,000 (range 62–332).[15]

The male to female ratio was lower in Asian studies (1–1.2) compared to 0.7–2.4 reported worldwide.[4] A higher male incidence (1.8; range 1.4–2) was also observed in another review of Western literature.[14]

There was an increase in the incidence rate beyond 50 years in all studies with a peak in the 7th and 8th decade.[4] The incidence rates continued to increase beyond 80 years in the Western studies, while it declined in the Asian studies.[4] This could be due to the

TABLE 2 Parkinson's disease incidence in Eastern and Western studies

Eastern studies	Crude incidence rate (per 100,000)	Age standardized to 2000 WHO population (per 100,000)	Western studies	Crude incidence rate (per 100,000)	Age standardized to 2000 WHO population (per 100,000)
Door to door surveys					
Wang YS et al, China (1991)	1.5	1.5	Baldereschi et al, Italy (2000)	346 (65–84 years) (1992–93)	27.6
Chen RC et al, Ilan,Taiwan (2001)	30.1 (>40 years)	8.7	deLau et al, Rotterdam, Netherlands (2004)	174.4 (55–85 years)	20.4
Das et al, Kolkata, India (2010)	4.56 (2003–08)	5.71	Benito-Leon et al, Spain (2004)	235.9 (65–85 years)	15.4
Record based surveys					
Morioka et al, Wakayama, Japan (2002)	16.9	8.3	Mayeux et al, New York, USA (1995)	13 (1988–93)	9.5
Tan LC et al, Singapore (2007)	33	6.7	Morens et al, Hawaii, USA (1996)	-	9.4
Liu et al, Taiwan (2016)	34.3 (2002–03) 36.6 (2008–09)	33.5 (2002–03) 36.6 (2008–09)	Van Den Eeden et al, Northern California, USA (2003)	12.3 (1994–95)	9.8
			Rajput et al, Rochester, USA (1984)		17.4
			Bower et al, Olmsted, Minnesota, USA (1976–90)		10.3
			Granieri et al, Ferrara, Italy (1991)	10.01 (1967–87)	6.1
			Foltynie et al, Cambridge, UK (2004)		8.2
			Mc Donald et al, London, UK (2000)	-	12.4
			Fall et al, Sweden (1996)	11	6.5

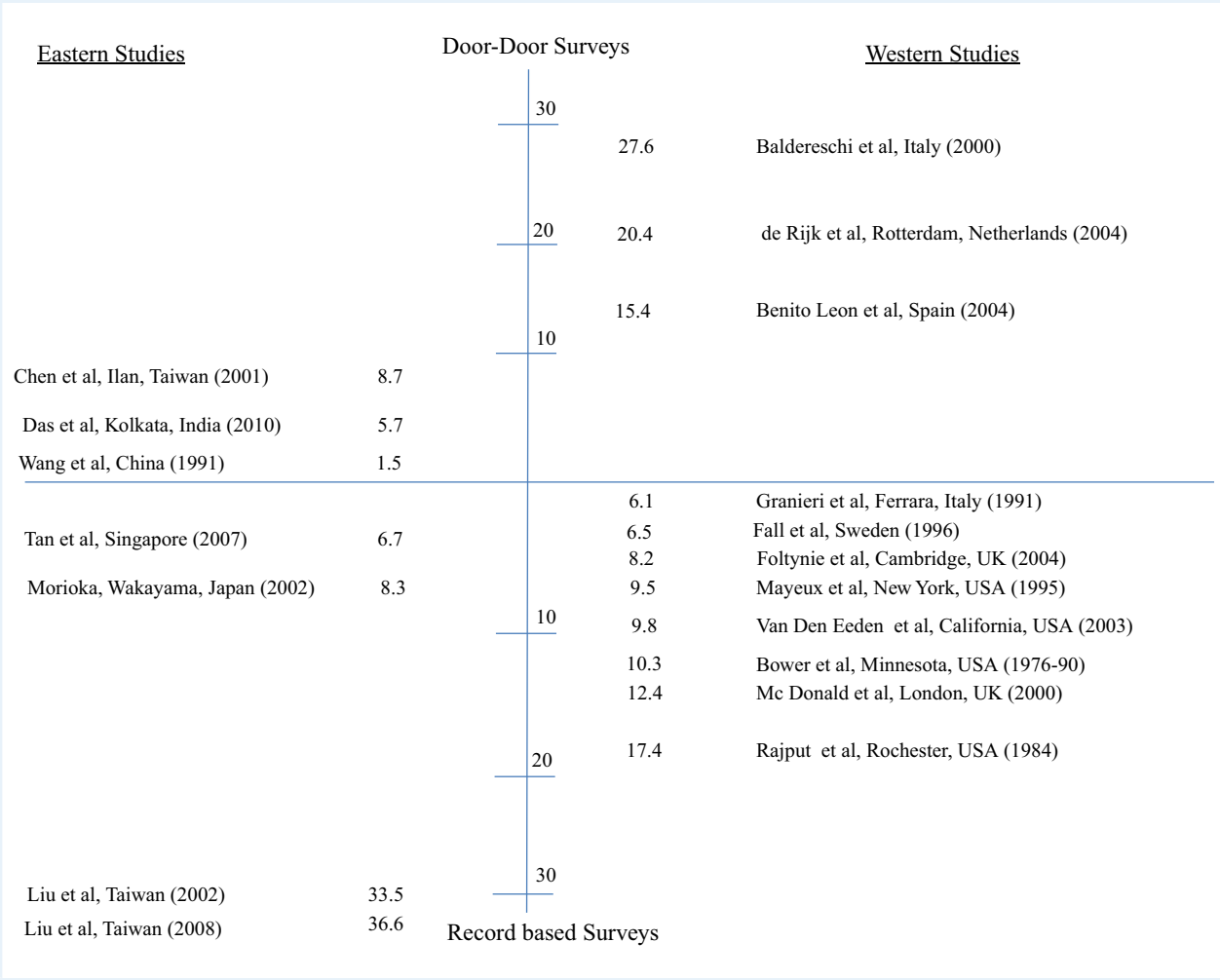

FIG. 2. Incidence of Parkinson's disease in Eastern and Western studies age standardised to 2000 WHO population (per 1,00,000).

smaller sample size, under diagnosis, restriction in assessing health care facilities, and difficulties in diagnosis due to the comorbidities.[4]

Ethnicity

Several record-based studies reported a lower PD prevalence in African Americans compared to Caucasians.[19,20] However, this was not seen in a community-based study.[21] The higher prevalence of PD amongst Caucasians could represent a genetic susceptibility, but could also be due to sampling bias resulting from socioeconomic and cultural factors.[22] As prevalence depends on incidence and survival, the reduced life expectancy in African Americans could also have led to lower prevalence rates.[22]

Interestingly, the prevalence rate for African Americans was higher than Africans in Nigeria studied using the same methods.[23] Similar higher incidence rate and prevalence pattern compared to the Asian studies were noted in American men of Japanese or Okinawan ancestry in a longitudinal study.[24] These studies suggest a role of environmental factors in the disease causation.

Amongst studies in Asia, a door-to-door survey among Parsi community in India found a higher prevalence rate compared to other studies from India favoring a genetic role in disease causation.[25] Ethnic variation in prevalence rates among Chinese, Malay, and Indians was however not observed in a study from Singapore.[26]

In incidence studies, the PD incidence was higher amongst Hispanics and Caucasians compared to African Americans and Asians in two record-based studies.[19,27] In another record-based study, PD incidence was higher in Caucasians and Latinos compared to African Americans.[28] A higher PD incidence in African Americans that was observed in only one study[20] was probably due to methodological differences. This study utilized the US census population, which may have underestimated the minority population, and increased the observed PD incidence amongst African Americans.[28]

Geographical Variation

Several studies have observed an increased prevalence and incidence of PD in the rural population[29–31]; while others have not

noted any difference.[16] An increased urban prevalence in PD was also observed in some studies.[19]

This variability could reflect geographical or methodological differences.[32] The environmental risk factors like pesticide exposure from agricultural practices in rural areas and industrial exposure to heavy metals in industrialized urban areas might contribute PD causation.[33] In a review of environmental risk factors in PD, Tanner et al suggested that rural living in developed countries and urban living in developing countries increased the risk of PD.[34]

The literature on time trends of PD is contradictory. A decreasing PD incidence over the past two decades was observed in the follow-up of the Rotterdam cohort from Europe.[35] However, the Rochester study from US has noticed an increasing trend over past three decades, particularly among males beyond 7th decade.[36] This could be related to the methodological issues like improvement in diagnosis, changes in diagnostic criteria, and selection bias. However, the differences could also reflect a change in exposures to environmental risk factors. The reduced PD incidence was attributed to an increase in smoking, coffee intake, and the use of statins.[35] The increased incidence could be related to reduced smoking rates among US males and differential exposure to risk factors like pesticides, head injury, and caffeine among the genders.[36] Three record-based surveys from East (1 Japan, two Taiwan) have noted an increased PD prevalence due to the ageing population. The PD incidence was stable over past 25 years in the Japanese study.[12] The two Taiwanese studies, using the National Health Insurance database, observed contradictory findings in the PD incidence rates over past 10 years, probably due to methodological issues.[10,13]

Analytical Epidemiology

The aim of our review is to highlight similarities, differences, and regional variations in risk factor exposure between the East and West. We have focused on the more established and well-studied non-genetic risk factors, risk factors unique to the East or the West, as well as emerging risk factors.

We performed a literature search via Pubmed up to May 2017 using the search terms "Parkinson's disease" and "risk factor" (separately), then "Parkinson's Disease and Risk factor." We also subsequently searched for individual risk factors using additional search terms, including "alcohol," "body mass index," "weight," "caffeine," "tea," "coffee," "dairy products," "cholesterol," "fat," "head injury," "pesticides," "physical activity," "exercise," "nicotine," "tobacco," "smoking," "uric acid," "urate," "hepatitis," "body mass index," and "weight." We searched for results that included original papers, review articles, and meta-analyses. In addition, reference lists of the relevant articles were screened. Only studies published in English were included and we focused on good quality studies and meta-analyses where available.

In comparing the East versus West results, we focused on the highest quality studies that were available from those areas. Being that the studies from the East showed fewer results, with lower quality studies across the range of risk factors, we decided to adopt a more inclusive approach and began to include case-control and cross-sectional studies as well. Readers are directed to other recently published reviews in this area, which have comprehensively discussed all risk factors relevant to PD.[5,37] A number of studies have attempted to weigh the strength of the various epidemiological factors associated with PD using various approaches.[5,38,39] These studies have concluded that the evidence for age as a causal relationship to PD is strong, with good evidence available for smoking and caffeine use. However, many of the other observed associations with PD remain probable or limited at best, with conflicting findings not uncommon due to marked methodological differences in defining and measuring the risk factor exposure. A summary of the major risk factors identified in Eastern and Western studies is presented in Table 3.

Smoking

The association of smoking and Parkinson's disease has been investigated in a large number of prospective cohort studies. It is well established as a protective factor for the development of PD. A recent meta-analysis evaluated eight cohort and 61 case-control studies performed over a 55-year period. The pooled RR of PD was 0.59 (95% CI: 0.56–0.62) for ever-smokers compared to never smokers, with a dose-response relationship demonstrated. The RR for smokers with more than 30 "pack-years" was 0.66 (95% CI, 0.49–0.88) compared with 0.39 (95% CI: 0.29–0.53) for those with less than 30 pack-years smoking history.[40] Results from the East and West have been consistent. Smoking as a risk factor for PD has been investigated using a weight of evidence assessment and compared against other risk factors—smoking has been the most consistent effect on PD risk.[41]

There are local variations in tobacco products available in the East and West. For example, snus is a moist powdered tobacco that is unique to the Sweden. It is a smokeless product that is usually placed under the upper lip. The association of PD and snus has been the subject of two pooled cohort studies in Sweden, which showed an adjusted HR, which ranged from 0.41 to 0.51 and was found to have an inverse dose related response on PD risk, which is similar to the pooled RR of cigarette studies obtained from the above-mentioned large meta-analysis.[40]

The beneficial effect of smoking is thought to be due to the potential therapeutic effect of nicotine, which has been shown to be neuroprotective in animal models of PD.[42] Nicotine-containing plants of the Solanaceae family, which includes peppers, tomatoes, potatoes, and eggplants has been investigated in a case-control study in Western Washington State.[43] These particular vegetables are present in large quantities in the Western "Mediterranean diet." PD risk was found to be inversely related to the consumption of Solanaceae family vegetables (RR 0.81, 95% CI: 0.65–1.01), with increased strength of association with nicotine concentrations of the individual vegetables.

TABLE 3 Summary of epidemiological risk factors for PD

	Eastern studies	Western studies
Cigarette smoking		
Cohort studies	A study in Singapore showed reduced risk for PD (RR 0.29, 95% CI: 0.16–0.52).[47]	7 studies performed in Greece, Netherlands and USA; all showed an overall reduction in RR of PD.[40]
Case-control studies	12 case-control studies performed in China, Hong Kong, India, Japan, Taiwan and Singapore. All studies showed an overall reduction in RR of PD. OR ranged from 0.38 to 0.85.[40]	50 case-control studies; the majority of studies showed an overall reduction in PD. OR ranged from 0.32 to 1.1 (only 2 studies obtained an OR of 1.0 and 1.1).[40,94]
Caffeine intake		
Cohort studies	1 cohort study performed in Singapore showed a reduced risk for PD (RR 0.55, 95% CI: 0.35–0.88).[47]	9 studies performed in Greece, Finland and the USA; the majority of studies showed an overall reduction in RR of PD (RR ranged from 0.39 to 1.49).[44,95–97]
Case-control studies	3 case-control studies performed in Japan and Singapore. All showed a reduction in OR for PD (OR: 0.45–0.78).[44,98]	14 case-control studies and 2 nested case-control studies: the majority of studies showed a reduction in RR for PD (RR: 0.17–1.26).[44]
Tea intake		
Cohort studies	1 cohort study performed in Singapore found that black tea consumption reduced PD risk (RR 0.29, 95% CI: 0.13–0.6). Consumption of green tea was unrelated to PD risk.[47]	3 cohort studies performed in Finland and USA. For tea consumption greater than 2 cups a day, 2 studies showed an overall reduction in RR of PD (RR: 0.40–1.21).[45]
Case-control studies	2 case-control studies performed in China and Japan: 1 study showed that both black tea (OR: 0.58) and Japanese/Chinese tea (OR: 0.59) consumption reduced PD risk[98] and 1 study found no association between tea consumption and PD risk.[48]	3 case-control studies performed in USA and Sweden; all showed an overall reduction in RR of PD (RR: 0.31–0.6).[45]
Pesticide exposure		
Cohort studies	Nil studies.	5 cohort studies from France, Hawaii, Netherlands and mainland USA; all showed an increased risk for PD (HR: 1.27–1.54).[50,99]
Case-control studies	6 studies from China, Hong Kong, Taiwan and India. The majority of studies showed an increased risk for PD (RR: 0.75–3.60).[48,50]	38 case-control studies. The majority of studies showed an increased risk for PD (RR: 0.8–7.0).[50,52,100,101]
Dairy products		
Cohort studies	Nil studies	5 studies performed in Greece, Finland and USA. All showed an increased RR for PD. The combined risk of PD for the highest versus the lowest level of dairy food intake for these 5 studies was RR 1.40 (95% CI: 1.20, 1.63).[55]
Case-control studies	1 case-control study performed in Japan found no association with PD risk.[57]	Nil studies
Urate		
Cohort studies	Nil studies	4 cohort studies performed in the Netherlands and the USA. 3 studies showed a reduction in RR of PD. RR ranged from 0.40 to 1.55.[60,102]
Case-control studies	Nil studies	2 nested case-control studies performed in the USA. All studies showed a reduction in RR of PD in men. RR ranged from 0.43 to 0.63.[60,103]
Dietary cholesterol		
Cohort studies	1 cohort study performed in Singapore. Compared to the lowest quartile, HR for the highest quartile of cholesterol intake was 0.53 (95% CI: 0.33–0.84) in men only.[66]	3 cohort studies performed in Netherlands and USA; all studies did not show an association between dietary cholesterol and PD risk.[104–106]
Case-control studies	1 case-control study performed in Japan found an increased risk for PD (OR 1.78, 95% CI: 1.04–3.05).[67]	2 case-control studies in USA. 1 study showed an increased risk (OR: 2.11), while another showed decreased risk of PD (OR: 0.53).[64,65]
Fats: total fats		
Cohort studies	1 cohort study performed in Singapore found no association with PD risk.[66]	2 cohort studies performed in the Netherlands and the USA. 1 study found a reduced risk per SD increase of energy-adjusted intake of 0.69 (95% CI 0.52–0.91) while the other study found no association with PD risk.[104,105]
Case-control studies	1 case-control study performed in Japan found no association with PD risk.[67]	1 case-control study performed in the USA found an increased risk for PD (OR 1.94).[65]

TABLE 3 (Continued)

	Eastern studies	Western studies
Monounsaturated fats		
Cohort studies	1 cohort study performed in Singapore showed a reduced risk in women only (HR 0.44, 95% CI: 0.22–0.88).[66]	3 cohort studies performed in the Netherlands and the US. 1 study found a reduced PD risk (HR 0.68, 95% CI: 0.50–0.94)[66]; 2 other studies did not find an association with PD risk.[105,106]
Case-control studies	1 case-control study in Japan found no association found with PD risk.[67]	Nil studies
Polyunsaturated fats		
Cohort studies	1 cohort study performed in Singapore found no association with PD risk.[66]	3 cohort studies performed in the Netherlands and the US, 2 studies found a reduced risk (RR: 0.65 and 0.66)[104,105]; and 1 study found an increased risk.[106]
Case-control studies	1 case-control study in Japan found consumption of arachidonic acid was associated with an increased risk of PD (OR 1.78, 95% CI 1.04, 3.05).[67]	Nil studies
Saturated fats		
Cohort studies	1 cohort study performed in Singapore found no association with PD risk.[66]	3 cohort studies performed in the Netherlands and the US. 2 studies did not show an association with PD risk.[104,106] 1 study showed an increased risk (RR 1.93, 95% CI: 1.10, 3.30) only in men.[105]
Case-control studies	1 case-control study in Japan found no association with PD risk.[67]	1 case-control study in the US showed an increased risk (OR 1.50, 95% CI: 1.07, 2.11).[64]
Mild traumatic brain injury		
Cohort studies	Nil studies	1 cohort study performed in Italy found no association of TBI with loss of consciousness with PD risk (adjusted OR 0.85, 95% CI: 0.45–1.66).[107]
Case-control studies	2 case-control studies performed in India and Taiwan; both showed an increased risk for PD (OR: 2.37–2.89).[68]	12 case-control studies performed in Australia, Brazil, Demark, Finland, Germany, Italy, Malta, Romania, Scotland, Sweden, United Kingdom and USA. The majority of studies (all except 3 studies) showed an increased risk for PD (OR: 0.61–4.75).[68]
Physical activity		
Cohort studies	Nil studies	7 cohort studies performed in Finland, Sweden and the USA. 5 studies showed a reduced risk of PD with increased physical activity; 2 studies showed a non-significant reduced risk of PD. HR ranged from 0.27 to 1.15.[78,108]
Case-control studies	2 case-control studies performed in China; both studies showed showed a reduced risk for PD (OR 0.20–0.48).[49,82]	1 case-control study performed in the USA showed that physical activity was associated with reduced risk for PD: OR 0.50 to 0.64 depending on the age in which the person engaged in physical activity.[109] 1 case-control study study performed in the USA showed that certain occupations associated with high physical activity was associated with reduced risk for PD.[110]
Body Mass Index (BMI)		
Cohort studies	Nil studies	9 cohort studies performed in Greece, Finland and the USA: most studies did not show an association between BMI and PD risk.[83]
Case-control studies	1 nested case-control study performed in China found an increased BMI was associated with lower risk for PD: RR 0.43 (95% CI 0.2–0.92).[111] 1 case-control study performed in Japan found a lower BMI in PD patients compared to controls.[112]	9 case-control studies performed in Argentina, Italy Spain, Sweden, UK and the USA: most studies found a lower BMI in PD patients.[84]
Alcohol		
Cohort studies	1 cohort study performed in Singapore found no association with PD risk.[87]	7 prospective cohort studies performed in Finland and the USA. The majority of studies did not find an association between PD risk and alcohol consumption (RR: 0.66–1.29).[87]

TABLE 3 (Continued)

	Eastern studies	Western studies
Case-control studies	3 matched case-control studies performed in China, Hong Kong and India found no association with PD risk.[87] 2 unmatched case-control studies performed in China and Japan. 1 study did not find an association between total alcohol consumption and PD risk but found that sake consumption was associated with increased PD risk,[87] another study found that frequent consumption of hard liquor was associated with decreased PD risk.[89]	14 matched case-control studies performed in France, Germany, Malta, Romania, Spain, Sweden, UK, USA. 5 studies showed a reduced risk of PD with alcohol consumption (RR: 0.27–1.01).[110] 5 unmatached case-control studies were performed in Spain, Sweden, USA. 2 studies showed no association of alcohol consumption with PD risk, 3 studies showed a reduced risk of PD with alcohol consumption, OR ranged from 0.36 to 0.80.[87]

Consumption of other non-Solanaceae vegetables was not associated with reduced PD risk.[43]

Caffeine

There is a convincing evidence that caffeine intake is associated with a lower risk of PD. A meta-analysis of 26 studies showed a relative risk of 0.75 (95% CI: 0.68–0.82).[44]

A subsequent dose-response meta-analysis was performed looking at the association between coffee and caffeine consumption at the risk of PD.[45] A non-linear relationship was found between coffee consumption and PD risk, with the strength of protection reaching the maximum at approximately 3 cups/day. East/West comparisons could not be made, as there was insufficient data from Asia. However, in the studies performed in the West, a stronger association between coffee consumption and PD risk was found in the studies performed in Europe when compared to the studies from the USA. A relative risk of RR 0.65 (95% CI: 0.56–0.74) for coffee consumption was obtained. A linear relationship was found between caffeine consumption with overall PD risk, with an RR 0.83% (95% CI 0.76–0.92) for every 200 mg/day increment of caffeine consumption.[45]

Tea

The association of tea consumption and PD has been the subject of at least two meta-analyses.[46] One recent meta-analysis which evaluated eight studies for tea consumption (four cohort studies, four case-control studies) obtained a summary relative risk of 0.63 (95% CI: 0.49–0.81), with the similar magnitude of risk reduction in the Eastern and Western studies.[45]

Black teas are consumed in both Eastern and Western cultures, while green teas are more common in the East. Black teas are fully fermented, resulting in high levels of caffeine but with lower levels of antioxidants. Green teas undergo minimal oxidation, with the process halted by panfrying in Chinese teas and steaming in Japanese teas. Oolong tea is partially fermented, hence contains more caffeine and more antioxidants than green tea.

In the East, there has been a prospective cohort study performed in Singapore, showing that black tea consumption was associated with a reduced risk of PD after adjusting for caffeine exposure, but consumption of green tea was not associated with PD risk reduction.[47] A subsequent case-control study performed in Japan which analyzed both green teas and oolong tea (partially fermented) together as a group suggested that consumptions of these Japanese and Chinese teas were associated with a reduced risk of PD (adjusted OR 0.59, 95% CI: 0.35–0.995). Oolong tea could have high fermentation and oxidization levels close to black tea, which could explain the discrepancy in findings between the Singapore and Japan studies. Another case-control study performed amongst the Uygur residents in China, where tea consumption is high, did not find an association between tea consumption and PD risk.[48]

A unique tea, yerba mate, which is an infusion made from dried, toasted, and milled leaves and stemlets of the *Ilex paraguariensis*, which is widely consumed in South American countries, was investigated in a case-control study in Argentina and was shown to have a similar risk reduction to conventional tea consumption with an OR of 0.64 (95% CI: 0.54–0.76).[49]

Pesticides

A recent meta-analysis on the relationship between pesticide use and PD evaluated 39 case-control studies, four cohort studies, and three cross-sectional studies. A summary relative risk of 1.62 (95% CI: 1.4–1.33) for pesticide exposure (ever vs. never) was found.[50] A positive association was observed with herbicides and insecticides, but not with fungicides. However, many of these studies were heterogeneous in the methodology used in the assessment of pesticide exposure. Another review, looking at the relationship between specific pesticides and PD, showed that there was a strong association between paraquat, rotenone, and organochlorides exposure with PD; but, the association between organophosphates, pyrethroids, and polychlorobiphenyl exposure was less clear.[51] Pesticide exposure has been largely studied in the context of occupational exposure; however, household exposure to all pesticides has also been shown in a case-control study from California to increase the odds of developing PD (OR 1.47, 95% CI: 1.13, 1.92).[52] Interestingly, exposure to household products containing organophosphates resulted in a higher risk of developing PD (OR 1.71, 95% CI: 1.21–2.41), which is broadly in line with estimated ORs from occupational exposures.[52] Novel epidemiological research techniques, utilizing Geographic Information System and satellite remote sensing data to calculate pesticide exposure, have been used to explore the association between pesticide exposure and PD incidence at the county level in Nebraska. It revealed that

exposure to certain pesticides such as alachlor and broxomy were significantly associated with PD incidence.[53] A small number of studies have been performed in the East, mainly in Hong Kong, Taiwan, and India. All, except one study, showed that pesticide exposure was associated with an increased risk of PD. Estimated RRs ranged from 0.75 to 3.60, which is broadly in step with data from the Western studies.[50]

An older review of the different cohort studies has suggested that well water drinking is a risk factor for PD in the West, but was found to be associated with a reduced PD risk in mainland China.[54] This difference was speculated to be due to the reduced use of pesticides and herbicides in mainland China. However, this might be no longer relevant with the modernization of China.

Dairy Products

A meta-analysis that looked at the association between the consumption of dairy products and PD evaluated five prospective studies.[55] The combined risk of PD for the highest versus the lowest level of dairy intake was 1.40 (95% CI: 1.20–1.63) overall (1.66 [95% CI: 1.29–2.14] for men and 1.15 [CI: 0.85–1.56] for women), with the strength of association higher in males than in females. Individuals with higher milk consumption were at higher risk. The linear dose-response relationship showed that PD risk increased by 17% (1.17; 95% CI: 1.06–1.30) for every 200 g/day increment in milk intake, and 13% (1.13; 95% CI: 0.91–1.40) for every 10 g increment in cheese intake.[55] Although pesticide contamination of milk could be a possible reason for the observed associations, the increased PD risk could also be attributed to the urate-lowering effect of dairy products.[56] However, a case-control study performed in Japan did not find an association between milk consumption and risk of PD, which could be attributable to the low levels of milk consumption.[57] In this particular study, the average dairy intake was very low in both the control and PD population group (around 150 g/day) when compared to the Western studies (around 700 g/day), which may not have allowed the effect of milk consumption to be properly observed in the Japanese population.[57]

Urate (Uric Acid)

Oxidative stress is thought to be a potential mechanism that underlies selective dopaminergic cell death in PD.[58] Urate is a potent antioxidant[59] and could be neuroprotective.

A number of studies have been performed looking at the association of uric acid and the risk of Parkinson's disease. A meta-analysis of three prospective cohort studies and a nested case-control study of three US cohorts obtained a pooled RR of 0.63 (95% CI: 0.42–0.95) in men and 0.89 (95% CI: 0.57–1.40) in women comparing the two extreme quartiles of urate.[60] Higher urate concentrations were found to be protective against PD risk in men, but not in women.[60] Similar findings were obtained in an earlier meta-analysis of four cohort studies performed in the Netherlands and the USA, and two nested case-control studies performed in the USA (RR 0.67, 95% CI: 0.50–0.91); with further subgroup analysis showing protective effects of serum urate in men, but not in women.[61]

Gout is a metabolic disorder that tends to occur in individuals with higher levels of serum uric acid, although other risk factors are also implicated. A nested case-control study was performed in the UK investigating the association of gout with the risk of PD.[62] A similar magnitude of effect was found which is consistent with the studies investigating the association of uric acid and PD. Individuals with a prior history of gout had a reduced risk of developing PD (OR 0.69, 95% CI: 0.48–0.99). Again, this association was seen in men (OR 0.60, 95% CI: 0.40–0.91), but not in women (OR 1.26, 95% CI: 0.57–2.81).[62]

A meta-analysis investigating the association of uric acid with a risk of PD evaluated 13 case-control studies performed in the East and West. Serum uric acid was found to be significantly lower in PD patients compared to controls. No difference was found between the East and West cohorts.[63]

Cholesterol

In the West, three prospective cohort studies performed in the Netherlands and the US did not find an association between dietary cholesterol and PD risk. The two case-control studies performed in the US found contradictory results—one study found that cholesterol intake decreased the risk of PD,[64] while another found that cholesterol intake increased the risk.[65] In the East, a prospective cohort study performed in Singapore found that dietary cholesterol in the highest quartile was associated with a lower risk of PD only in men when compared to the lowest quartile, HR (95% CI) for the highest quartile was 0.53 (95% CI: 0.33–0.84).[66] However, a case-control study performed in Japan found the reverse and that dietary cholesterol was associated with an increased risk of PD.[67] The discrepancy of findings among various studies might be due to methodological issue like using food dairies which are prone to recall bias, also they cannot accurately estimate amount of cholesterol in wide range of foods. This might explain some of the discrepant findings across various studies.

Dietary Fats

The role of dietary intake of the various fats has been investigated in a small number of prospective cohort studies and case-control studies both in the East and West. Overall, the results from the various studies have yielded conflicting results and gender differences. At present, there is no convincing evidence that dietary intake of total fat or different fats are associated with PD risk (Table 3).

Mild Traumatic Brain Injury

Severe traumatic brain injury (TBI) is a well-established risk factor for neurodegenerative diseases, including PD. Recent

studies have focused on the role of mild TBI as a risk factor for neurodegenerative disease. A meta-analysis looked at the association between mild TBI and the development of neurological and psychiatric disease.[68] Fourteen case-control studies and one cohort study were evaluated for the association between mild TBI and PD. A summary relative risk of OR 1.45 (95% CI: 1.18–1.78) for mild TBI was found. An increased risk of PD with TBI was largely noted in the case-control studies and not in the cohort study. This was probably due to a limited number of patients (n = 8) in the cohort study and the fact that it only included head injury patients with a loss of conciousness.[69] The two Asian (India, Taiwan) studies in this meta-analysis noted an increased PD risk with head injury (ORs of 2.37 and 2.89, respectively).[70,71] However, in both these studies, patient numbers were small and it could not be ascertained whether the reported head injury was also accompanied by loss of consciousness. Findings from another meta-analysis were similar.[72] The definition of mild TBI is highly heterogeneous across the different studies (some studies required associated loss of consciousness while some did not), with few high-quality studies[73] and reverse causation have been hypothesized to lead to the reported positive associations.[74] A recent large interview-based case-control study performed in Denmark did not find an association between head trauma and PD.[75] The risk of PD following mild TBI remains unclear (Table 3).

In the East, Thai traditional boxers were studied for the risk of developing PD. The crude prevalence of PD was estimated to be 0.71%, however, that increased to 0.98% in boxers who were aged 50 years or more and had an increased number of professional bouts, suggesting that repetitive head trauma is a risk factor for the development of PD.[76] In the West, an often-quoted study published in 1969 estimated a much higher rate—17% of the sampled boxers showed neurologic deficits attributable to boxing.[69] However, due to recent changes to the rules of play, the use of protective equipment, and the duration and intensity of boxing careers, this data is difficult to apply to modern day boxers. No recent studies are available in the West that look at the risk of PD resulting from boxing. A registry study performed in the US that looked at the causes of mortality in professional football players showed that mortality from PD was increased (SMR with PD listed as the underlying cause was 2.14, with PD listed as the contributory cause was 1.69), but did not reach statistical significance.[77]

Physical Activity

A meta-analysis investigating the association between physical activity levels and risk of PD evaluated six cohort studies. A summary risk estimate of HR 0.66 (95% CI: 0.57–0.78) for the highest versus the lowest physical activity level was obtained.[78] Although reverse causation could be a possible cause for the observed associations, the findings of increased physical activity during high school and college,[79] or at ages 35–39 years,[80] being associated with a reduced risk of subsequent late-adult life development of PD, instead supports a possible neuroprotective effect of physical activity.[81] The association of physical activity and risk of PD has been recently investigated in two Eastern case-control studies from China. A reduced PD risk was observed in both the studies.[48,82]

Body Mass Index (BMI)

The association of body mass index (BMI) and risk of PD has been the subject of two meta-analyses. The first meta-analysis evaluated 10 prospective studies and did not find an increased risk for PD: obtaining a summary RR of 1.00 (95% CI 0.89, 1.12) for every 5 kg/m^2 increase in BMI. However, there was significant heterogeneity amongst the studies for adjustment of confounders and many of these prospective studies had only obtained single measurement of weight at baseline. Weight changes during the course of follow-up were not accounted for, and differences in PD risk were obtained depending on whether BMI measurements were taken at baseline or nearer the clinical diagnosis of PD.[83] Another meta-analysis that approached this question with a different methodology evaluated 12 case-control studies in which body weight was objectively measured. This meta-analysis found that PD patients had a significantly lower BMI compared to controls: OR 1.73 (95% CI 1.11, 2.35).[84] More recently, a large multicentre Mendelian randomization study, which included large study sites from the West and one site from the Philippines, found that a higher BMI was associated with a lower risk of PD (OR 0.82, 95% CI 0.69, 0.98).[85] The association of BMI with PD risk remains complex and controversial.

Alcohol

The association of alcohol intake and the risk of Parkinson's disease has been the subject of one meta-analysis and one review paper.[86,87] The meta-analysis of 32 studies (eight prospective cohort, 17 matched case-control, and seven unmatched case-control studies) found that alcohol intake could be associated with reduced Parkinson's disease risk, with a stronger association found in studies performed in Europe compared to studies from the United States and Asia.[86] In another meta-analysis, a weak protective association tended to be reported in case-control studies rather than prospective cohort studies.[87] In a prospective study from Sweden, heavy alcohol use was associated with an increased risk of PD (HR 1.38, 95% CI: 1.25–1.53, adjusted for age and sex).[88]

The studies performed in the East did not find an association between alcohol intake and PD risk. The prospective cohort study from Singapore found a non-significant decreased risk (RR 0.6, 95% CI: 0.31–1.16) in "at least weekly drinkers" compared to "none," or "less than weekly" drinkers.[87] One case-control study from Japan did not find a significant association between total alcohol consumption and PD risk.[89] However, among the different types of alcohol, only Japanese sake (rice wine) was significantly associated with increased PD risk (adjusted or of ≥66 g ethanol per day; 3.39, 95% CI: 1.10–11.00).[89]

The reporting of alcohol consumption is subject to selection and recall bias and could account for the differences observed. Alcohol is thought to exert its protective effect by elevating urate levels. Overall, the association between alcohol consumption and PD risk is modest.

Hepatitis C

The association between the Hepatitis C virus infection and risk of PD has been the subject of a recent review, evaluating three large retrospective cohort studies including two nationwide studies and one case control study, with all studies consistently showing an increased risk for PD.[90] Findings from studies in the East have shown an association between only Hepatitis C infection and PD; whereas one retrospective cohort study from the UK found an association between the Hepatitis B and C virus infection with PD, but not with other forms of hepatitis.[91] Large nationwide health-insurance database and large regional screening programs for Hepatitis, implemented in Taiwan, have enabled this previously unknown association between the Hepatitis C virus and PD to be described,[92] findings of which have been recently replicated in the West in a nationwide UK study, utiliaing the UK HES database.[93]

Mechanisms proposed for the association include, direct Hepatitis C virus infection of the brain and interferon induced Parkinsonism. The Hepatitis C virus has been shown in mouse models to induce neuronal toxicity similar to that of 1-methyl-4-phenylpyridinium (MPP+).[91] Prospective cohort studies have yet to be performed and further studies are necessary to clarify the potential contributory role of interferon treatment and PD, which has been reported in isolated case reports to induce parkinsonism.

Conclusions

In summary, Parkinson's disease is more common with increasing age in both the East and West. It is 1.5–2 times more common in males than females, although this difference was less noticeable in Asian studies.[5] PD appears to be less prevalent in Asian countries than Western ones, although there is some overlap in the range of prevalence rates.[4–8] Leaving methodological issues aside, these differences could be explained by a combination of environmental and genetic risk factors.[6,11] PD incidence is also lower in Asian countries compared to Western ones; although a definite conclusion could not be drawn due to the small number of Asian studies.[4] Incidence studies on different ethnic populations in the same country have also found a lower occurrence of PD amongst Easterners (Asians and Africans) compared to Westerners (Caucasians, Hispanic, Latinos). This finding suggests a genetic influence on the risk of developing PD. However, the higher occurrence of PD among African Americans[23] and Japanese Americans[24] when compared to similar populations in their native country, suggest an environmental role in PD.

Overall, there have been a large number of epidemiological studies performed both in the East and West investigating the risk factors for Parkinson's disease. However, most studies in the East have been limited to case-control studies, with few large prospective cohort studies. For the well-established risk factors, in particular, smoking, caffeine intake, and pesticide exposure, both in East and West studies have largely shown consistent results; and local variations in exposure to risk factors, unique to certain geographic regions (such as the snus in the Sweden and yerba mate consumption in Argentina), have also shown similar effects on the risk of PD. Dairy product consumption, urate levels, and physical activity have been well studied in Western cohorts but have not been well studied in the East. With regards to alcohol, fat consumption, and BMI, findings in both the East and West have been mixed and conflicting. Recent findings regarding the association of the Hepatitis C virus infection and PD warrant further study.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

M.M.A.: 1B, 1C, 2A, 2B, 2C, 3A, 3B
Z.X.: 1B, 1C, 2A, 2B, 2C, 3A, 3B
L.T.: 1A, 1B, 1C, 2A, 2B, 2C, 3A, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflict of Interest: This research is supported by the Singapore National Research Foundation under its Translational and Clinical Research Flagship Programme (TCR12dec010) and administered by the Singapore Ministry of Health's National Medical Research Council. The authors report no conflicts of interest.

Financial Disclosures from previous 12 months: None.

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